

**REMARKS**

Claims 1-13 are pending in this application. Claims 1-5 were previously canceled, leaving claims 6-13 remaining. Claims 6-9 have been amended.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 4 to page 13; in claims 1-13 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

**1. Rejection of Claims 6-13 under 35 U.S.C. §112,  
first paragraph**

The Office Action rejects claims 6-13 under 35 U.S.C. §112, first paragraph relating to enablement. The examiner admits that the Specification is enabling:

"only for a method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5, does not reasonably provide enablement for a method for preparing a reagent for use

in diagnosing schizophrenia and a method of diagnosing schizophrenia using proteins or fractions from platelet wherein the pI of the proteins or fractions is greater than or equal to about 6.5 as set forth in claims 6-13."

The Office Action rejects claims 6-13 because the Specification does not reasonably provide enablement for "any" methods as set forth in claims 6-13 for diagnosis of schizophrenia in an individual, and states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the following reasons:

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI

of said proteins or fractions thereof is within the range of about 6.5 to about 9.5.

The specification does not teach the claimed methods as set forth in claims 6-13 because there is insufficient guidance as how to make any platelet proteins or fractions thereof wherein the "pI is greater than or equal to about 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of about 6.5 to about 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is insufficient guidance and in vivo working demonstrating that all proteins fractions having a pI greater than 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the specification does not disclose the platelets proteins or fractions equal to about 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. The specification discloses the diagnostic method does not work when the pI is lower than 6.5. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

Further, not only there are more than one platelet proteins associated with any one specific pI, there is insufficient guidance as to the molecular weight of any platelet proteins associated with that particular pI, let alone the structure associated with function of any platelet proteins for the claimed diagnostic method. A platelet protein without the molecular weight associated with the specific amino acid sequence has no structure, much less function.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational

of the protein (See enclosed appropriate pages).

Applicants have not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the various platelet proteins for the claimed method. While protein having a range of pI of above about 6.5 or a pI within the range of above 6.5 to about 9.5 may have some notion of the activity such as induces DTH, claiming a method of injecting platelet proteins fails to distinctly claim what that proteins are and what the compositions are made up of for the claimed method. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any platelet proteins for the claimed diagnostic method other than the isolated platelet or platelet proteins fraction having a pI in the range of 6.5 to 9.5 as disclosed on page 12 of the specification.

Given the indefinite number of undisclosed platelet proteins having a pI of above about 6.5 or within the range of above 6.5 to about 9.5, it is unpredictable which undisclosed platelet proteins is useful for the claimed method of diagnosing schizophrenia in a subject. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

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In response, the specification does not teach the claimed methods as set forth in claims 6-13 because there is insufficient guidance as how to make any platelet

proteins or fractions thereof wherein the "pI is greater than or equal to about 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of 6.5 to 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is insufficient guidance and in vivo working demonstrating that all proteins fractions having a pI greater than 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the term "equal to about 6.5" renders the range unclear. No where in the specification discloses the platelets protein fraction equal to 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pl. The specification discloses the diagnostic method does not work when the pI is lower than 6.5. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pl: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

Applicants again thank the Examiner for the acknowledgment of enablement of the subject matter described above, which is the subject matter of claims 10-13. The Examiner having admitted that claims 10-13 are enabled, Applicants further address only claims 6-9.

Applicants thank the Examiner for the courtesy extended during the interview held on June 29, 2004. In accordance with the discussions held at the interview, Applicants have amended the claims in the expectation that the amendments will overcome the

rejections under 37 U.S.C. §112. In particular, it was agreed that the amendments presented herein, limiting claims 6-9 to recite a pI "greater than about 6.5," would overcome the rejections under 35 U.S.C. §112.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

**2. Rejection of Claims 6-13 under 35 U.S.C. §112,  
first paragraph**

The Office Action further rejects claims 6-13 under 35 U.S.C. §112, first paragraph relating to written description for the following reasons:

The specification does not reasonably provide a written description of a method for preparing a reagent for use in diagnosing schizophrenia and a method of diagnosing schizophrenia using proteins or fractions from platelet wherein the pI of the proteins or fractions is "greater than or equal to about 6.5 as set forth in claims 6-13.

The specification discloses only method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5.

Other than the specific isolated platelet or platelet proteins fraction having a pI within the range of 6.5 to 9.5 for the claimed methods, there is insufficient written description about the structure associated with function of any platelet proteins or fractions wherein the pI is "greater than or equal to about 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of about 6.5 to about 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is inadequate written description about all proteins fractions having a pI greater than 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the term "equal to about 6.5" renders the range unclear. No where in the specification discloses the platelets protein fraction equal to 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

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Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph relating to written description.

**3. Rejection of Claims 6-13 under 35 U.S.C. §112,  
first paragraph**

The Office Action rejects claims 6-13 under 35 U.S.C. §112, first paragraph as having new matter, for the following reasons:

The "the pI of said proteins or fractions thereof is greater than about 6.5" in Claims 6-9 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 1/6/04 do not provide a clear support for the said phrase.

Applicants thank the Examiner for the courtesy extended during the interview held on June 29, 2004. In accordance with the discussions held at the interview, Applicants have amended the claims in the expectation that the amendments will overcome the rejections under 37 U.S.C. §112. In particular, it was agreed that the amendments presented herein, limiting claims 6-9 to recite a pI "greater than about 6.5," would overcome the rejections under 35



U.S.C. §112.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the new matter rejection under 35 U.S.C. §112, first paragraph.

**4. Rejection of Claims 6-13 under 35 U.S.C. §103(a)**

The Office Action rejects claims 6-13 under 35 U.S.C. §103(a) as being unpatentable over WO 97/13152 publication (or record, April 1997; PTO 1449) in view of Jankovic et al (J Immunol 135(2 suppl): 583s-587s, Aug 1985, PTO 892), Ovary et al (Adv Biol Skin 11: 103-21, 1971; PTO 892), and Rotman et al (Prog Neuropsychopharmacol Biol Psychiatry 7(2-3): 135-41, 1983; PTO 1449). As the basis for this rejection, the Office Action states:

The WO 97/13152 publication teaches a method for preparing a reagent for diagnosis of dementia comprising the steps of obtaining blood from a number of individuals or individual such as demented patients or healthy normal subjects, isolating platelet from the said blood samples (See entire document, page 8 in particular), preparing a protein fraction from the reference platelet preparation comprising proteins such as 75 kD platelet protein and platelet associated antibodies against said 75 kD platelet protein by isoelectric focusing, (See page 10, abstract, summary of invention, in particular) wherein said proteins have a pI between 7 and 9, which is greater than about 6.5 (See page 12, Fig 4). The reference pI is within the claimed range of above 6.5 to about 9.5.

The claimed invention in claim 6 differs from the teachings of the reference only that the method for the preparation of a reagent for use in diagnosis of schizophrenia instead of dermentia by obtaining blood sample from a number of individuals, collecting platelets

from the pool of blood samples, preparing proteins fraction from said platelets wherein the pI of the said proteins or fractions thereof is greater than or equal to about 6.5.

The claimed invention in claims 7 and 9 differs from the teachings of the reference only that the diagnostic method for determining schizophrenia instead of dementia in an individual by obtaining a platelet protein preparation comprising platelet derived proteins wherein the pI of said proteins is greater than or equal to about 6.5, injecting into a subject said platelet proteins and examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

Jankovic et al teach a diagnostic method for determining schizophrenia in a subject by detecting a delayed type hypersensitivity reaction to a human brain antigen such as brain S-100 protein and the high incidence of positive skin DTH reaction to the reference protein in schizophrenia indicates that cell-mediated immune processes may be involved in schizophrenia (See abstract, in particular).

Ovary et al teach that the principal reason for the use of skin as a tool to study immunological phenomena because of its convenience. Skin has been used for decades to study allergic and immunologic response because skin reactions are easy to produce and observe and in many cases can be extremely sensitive in demonstrating sensitization (See page 103, 1st paragraph, in particular).

Rotman et al teach blood platelets are a very good model for nerve endings, serotonin uptake and imipramine binding and the efficiency of various drugs such as antidepressants have been evaluated using blood platelets instead of synaptosomes (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a protein fraction from platelets wherein protein fractions having a pI between 7 and 9 as taught by the WO

97/13152, and substituting the brain S-100 antigen taught by Jankovic et al for the platelet proteins fractions as taught by the WO 97/13152 and Rotman et al for a method of diagnosing schizophrenia in an individual by detecting a DTH as taught by Jankovic et al and Ovary et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Ovary et al teach that the principal reason for the use of skin as a tool to study immunological phenomena because of its convenience. Skin has been used for decades to study allergic and immunologic response because skin reactions are easy to produce and observe and in many cases can be extremely sensitive in demonstrating sensitization (See page 103, 1st paragraph, in particular). Rotman et al teach blood platelets are a very good model for nerve endings, serotonin uptake and imipramine binding and the efficiency of various drugs such as antidepressants have been evaluated using blood platelets instead of synaptosomes (See abstract, in particular). Kessler et al teach platelets from schizophrenic patients bear autoimmune antibodies that inhibit dopamine uptake and that platelets could possibly serve as the peripheral trigger for an autoimmune reaction that eventually propagates to the CNS (See abstract, page 300, column 1, 1st paragraph, in particular). Jankovic et al teach that a high incidence of positive skin DTH reaction indicates that cell-mediated immune processes may be involved in schizophrenia (See abstract, in particular).

Applicants respectfully traverse this rejection for the reasons stated in the Responses previously filed in this matter, and for the following additional reasons. As previously described, in order to establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d

1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Second, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Third, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). The outstanding rejection meets none of these requirements.

Of particular import from the previous Response, Applicants note that the Declaration of Meir Shinitzky, who is a co-inventor named in the present application, a co-inventor named in the cited WO 97/13152 application, a co-author of the cited Kessler, et al. (Dementia) publication, and as a person having personal knowledge of the work described in the cited Burbaea/Yankovich publication, was previously filed. In the Declaration, Dr. Shinitzky described in detail her own work relating to the cited WO 97/13152 application. In brief, WO 97/13152 clearly stated that the 75 kD platelet-protein and the related platelet associated antibodies, which were disclosed in WO 97/13152 to be associated with multi-

infarct dementia and dementia of the Alzheimer type, are not the same as the isolated platelet-proteins or fractions thereof having a pI above about 6.5, which are claimed in the present application.

The Examiner has argued that the Declaration is insufficient, but has not provided any contrary evidence or reasoning for the refusal to accept the signed Declaration of an inventor with personal knowledge of the facts stated therein. The USPTO should not place itself in the position of rejecting a sworn Declaration without substantial reasons. Contrary to the Office Action, the undisputed evidence before the Examiner shows that WO 97/13152 teaches the use of different proteins for screening for a different disorder, and thus teaches nothing whatsoever about the claimed inventive subject matter.

At the outset, it is noted that there are four references cited and combined to reach the rejection of the inventive subject matter under §103. Applicants first observe that although there is no firm rule, it is generally accepted that the need to combine more than two or three references tends toward a conclusion of non-obviousness.

The primary reference is the inventors' own work, PCT Publication No. WO 97/13152, published 10 April 1997. WO 97/13152 discloses an assay for the diagnosis of dementia and Alzheimer's disease, involving determination of the level of a 75 kD platelet

protein and platelet-associated antibodies ("PAA") to the 75 kD protein. WO 97/13152 does not teach or suggest that platelet proteins might be useful in an assay for schizophrenia.

A secondary reference is Jankovic, J. Immun. 135:853s-856s. Applicants respectfully submit that Jankovic teaches that there is a correlation, shown in Tables 1 and 2, between several psychiatric disorders and skin hypersensitivity to **brain S-100 protein** and to **neuron-specific enolase** ("NSE"), as a result of the presence of circulating antibodies to these two proteins. Jankovic also makes the broad statement that there is a correlation between immunopsychiatric disorders and delayed hypersensitivity to **neural tissue antigens** generally. However, Jankovic does not teach or suggest that the level of **platelets** or **platelet associated antibodies** is in any way related to psychiatric disorders, and there is no teaching or suggestion, in Jankovic or as a part of the general knowledge in the art, that (1) platelets are neural tissue, or that (2) platelet associated antibodies are neural tissue antibodies. Indeed, even a general understanding of what platelets are and what neural tissues are, would lead one of ordinary skill to the conclusion that they are not related in any way, at least in the absence of some teaching or suggestion to the contrary.

Another secondary reference is Rotman, Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 7:135-151. Applicants respectfully submit that Rotman teaches that platelets are a good model for the uptake by neuronal tissues of serotonin and imipramine, but not dopamine or norepinephrine, and as a tool for testing neuropharmaceuticals. More specifically, Rotman teaches that the  $K_m$  for platelet serotonin uptake in normal and schizophrenic subjects is unchanged, while  $V_{max}$  for schizophrenic subjects is 35-40% lower than normal subjects. Similarly, Rotman teaches that there is a correlation between a decrease in the number of  $\alpha$ -adrenergic receptors and the incidence of schizophrenia. Applicants respectfully submit that this data, showing the same individual transporter kinetics but lower overall transport, demonstrates that there are simply fewer serotonin transporters and  $\alpha$ -adrenergic receptors in schizophrenic subjects. Further, Rotman also suggests that platelet shape changes are correlated with serotonin uptake and perhaps neuronal disorders.

However, what Rotman does not teach or suggest that there is any correlation between the number of normal serotonin transporters and  $\alpha$ -adrenergic receptors, and the number of platelet proteins or the quantity of antibodies to such proteins. Indeed, it is counter-intuitive to interpret Rotman as suggesting that one of ordinary skill in the art would expect an enhanced immune response

to fewer transporters without a specific teaching to that effect. Nor does Rotman teach or suggest that shape changes in platelets are in any way related to an enhanced immune response; again, it is counter-intuitive to reach such a conclusion without a specific teaching to that effect. Further, whether Rotman teaches that platelets are a good tool for testing neuropharmaceuticals is irrelevant to the problem, which is diagnosis--not treatment--of Schizophrenia.

The third secondary reference is Ovary, et al. Applicants respectfully submit that Ovary, et al. teach only that skin is a good milieu for the study of delayed hypersensitivity responses. Ovary, et al. do not teach or suggest anything to the effect that platelet proteins might be useful in an assay for schizophrenia.

Thus, Applicants respectfully submit that the cited references do not teach all elements of the inventive subject matter.

Further, the Office Action fails to meet the additional requirement to support a *prima facie* case of obviousness: there must be an objective, clear, and particular teaching or suggestion, found in the cited reference(s), in general knowledge of special interest or importance in the art, or from the nature of the problem to be solved, which would lead one of ordinary skill in the art to combine references, with a reasonable expectation of success and without defining the problem to be solved in terms of an



Applicant's solution (i.e. using improper hindsight), to reach the inventive subject matter. (*In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999); *Sibia Neurosciences Inc. v. Cadmus Pharmaceutical Corp.*, 225 F.3d 1349, 1356-1357, 55 U.S.P.Q.2d 1927, 1931 (Fed. Cir. 2000); *In re Rouffet*, 149 F.3d 1350, 1358, 27 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998); and *In re O'Farrell*, 853 F.2d 894, 902, 7 U.S.P.Q.2d 1673, 1680 (Fed. Cir. 1988)). Applicants respectfully submit that they have carefully reviewed the cited references and can find absolutely no teaching or suggestion that any of the cited references should be combined. Further, the Examiner has cited no general knowledge of ***special interest or importance*** in the art. And there is no evidence or reasoning that the nature of the problem to be solved, finding a method for diagnosing schizophrenia, would prompt one of ordinary skill in the relevant to look a platelet-related solution.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

#### **CONCLUSION**

Based upon the above remarks, the presently claimed subject matter is believed to be enabled, sufficiently described, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and

withdraw the rejections of remaining claims 6-13 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

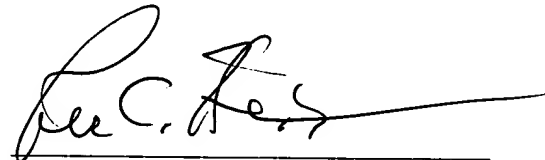
The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

**NATH & ASSOCIATES PLLC**

Date: October 21, 2004

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